

BS 24. A humanized mature heavy chain variable region having a sequence designated SEQ ID NO:10.

REMARKS

The amendments to the specification and claims serve to clarify terminology used to describe immunoglobulin chains. As the Examiner is doubtless aware, both heavy and light chain immunoglobulins are initially expressed as pre-proteins containing leader signal sequences. The signal sequences are then cleaved, resulting in mature heavy and mature light immunoglobulin chains.

In the present application, Fig. 1A and Fig. 1B depict the sequences of the light and heavy chains, respectively, of the mouse AF2 immunoglobulin. Fig. 2A and Fig. 2B depict the sequences of the light and heavy chains, respectively, of humanized AF2. Both Fig. 1A and Fig. 1B and both Fig. 2A and 2B include leader signal sequences. The humanized heavy chains of AF2 shown in Fig. 3 depicts only the mature heavy chain residues. Thus, the heavy chain sequence designated HuZaf in Fig. 3 is the same as the heavy chain sequence in Fig. 2B, except that the latter also includes a signal sequence.

The first residue of the mature mouse AF2 and humanized AF2 light chains shown in Figs. 1A and 2A, respectively, occurs at residue 21. Such is readily apparent from comparing these sequences with that of the mature humanized light chain of AF2 shown in Fig. 32A of WO 92/11018 (incorporated by reference into the present application). The first residue of the mature mouse and humanized heavy chains shown in Figs 1B and 2B occurs at residue 20. Such is readily apparent by comparing these sequences with that of the mature heavy chain designated HuZaf in Fig. 3, as mentioned above.

Thus, Applicants have amended the Brief Description of Figs. 2A and 2B to be consistent with the Figs. 2A and 2B themselves, which include the leader signal

sequences. This amendment merely conforms the Brief Description to the Figures and does not, therefore, constitute new matter.

Applicants have also amended the Brief Description of Fig. 3 to make even more clear that the humanized heavy chains depicted in Fig. 3 are mature chains (i.e., lack a leader signal sequence). Again, this amendment merely conforms the Brief Description to the Figure and does not, therefore, constitute new matter.

Claims 14 and 15 have also been amended to define the mouse AF2 antibody by the mature variable regions of SEQ ID NOS: 2 and 4 rather than the complete sequences (which include the leader signal sequences). Although an antibody can be adequately defined by either the complete pre-protein sequences containing leader signal sequences or the mature sequences without leader signal sequences, definition by the mature sequences is more conventional as it is these mature sequences that are permanently present in an antibody once it has been secreted from a cell. The Examiner will note that this is the manner in which the humanized immunoglobulin of independent claim 17 is already presently defined. This amendment does not add new matter.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION:**

The paragraph beginning on page 5, line 8 has been amended as follows:

Fig. 2A and 2B: cDNA (SEQ. ID. Nos. 5 & 7) and amino acid (SEQ. ID. Nos. 6 & 8) sequences of the [mature] variable regions of light and heavy chains of humanized antibody HuZAF. Kabat CDRs are underlined.

The paragraph beginning on page 5, line 12 has been amended as follows:

Fig. 3: Comparison of the mature heavy chain variable region amino acid sequence of mouse AF2, humanized immunoglobulin HuZAF and humanized immunoglobulins QAF2, haf25, and X.

**IN THE CLAIMS:**

Claim 14 was amended as follows:

14. (Amended) A humanized immunoglobulin, which is a humanized version of the mouse AF2 immunoglobulin having a mature light chain variable region of [designated] SEQ ID No:2 and a mature heavy chain variable region of [designated] SEQ ID No:4, the humanized immunoglobulin comprising humanized heavy and light chains, provided that position 11 according to the Kabat numbering system of the humanized heavy chain variable region framework is occupied by the amino acid present in the equivalent position of the mouse AF2 heavy chain variable region framework.

Claim 15 was amended as follows:

15. (Amended) A humanized immunoglobulin, which is a humanized version of the mouse AF2 immunoglobulin having a mature light chain variable region [designated] of SEQ ID No:2 and a mature heavy chain variable region [designated] of

SEQ ID no:4, the humanized immunoglobulin comprising humanized heavy and light chains, provided that position 11 according to the Kabat numbering system of the humanized heavy chain variable region framework is substituted with the amino acid present in the equivalent position of the mouse AF2 heavy chain variable region framework.

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